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Assessment of Quality Control Parameters of Aceclofenac Sustained Release Tablets Marketed in Nepal

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Abstract

Introduction: Aceclofenac has rate-limiting dissolution steps, lower solubility and higher permeability physical properties. Different brand products of same drugs require analysis for their biopharmaceutical equivalence to ensure efficacy and their safety.

Objective: This study aims to analyses biopharmaceutical and physicochemical equivalence of different trade of sustained release Aceclofenac tablets manufactured in Nepal.

Method: A cross-sectional study with sustained release tablets of Aceclofenac from Eight different manufacturer were collected and analyzed for their biopharmaceutical and physicochemical properties through two standards and established methods. Descriptive statistics were calculated.

Result: The weight variation of all brands ranged within the maximum limit of ±5% except brand H. Most of the brands had the recommended hardness (≥4Kg/cm^2). The friability values of all products were within the recommended specification (≤1%). Assay conducted for all tablets revealed that they contain medicine ranging between 85-115% which indicate that all tablets pass the test for assay. The percentage drug release of all brand was in the range of 50 – 80% except brand E showed 63.88% drug release in 8th hour. The brand A, B and H followed pappes release model of kinetic and brand C followed zero order kinetic whereas brand D and G followed first order kinetic model and brand E & F followed Higuchi model.

Conclusion: All brands except one were interchangeable in terms of biopharmaceutical equivalence and sustained release formulation. Further, more in-vivo bioequivalent studies should be conducted to correlate the findings.

Keywords: Aceclofenac, Quality assessment, Sustained release

Introduction

Aceclofenac belongs to a non-steroidal anti-inflammatory drug (NSAIDs). It exerts the property of antipyretic, analgesic and anti-inflammatory which is beneficial in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.[1,2] For the same but prolonged action Aceclofenac sustained release (SR) tablet of 200 mg is administered. The mechanism of action of aceclofenac include the inhibition of cyclo-oxygenase enzyme which facilitate the production of prostaglandin responsible for fever, pain and inflammation.[3-5] Use of SR formulation of Aceclofenac leads to reduction in frequency of dosing, uniform drug release over time and better patient compliance.[6-8] The demerits of Aceclofenac sustained release tablets are high cost, dose related toxicity and often unpredictable correlation of in-vitro and in-vivo.[9,10]

As per biopharmaceutics classification system, Aceclofenac is class II which means low solubility, high permeability and poor dissolution property.[11,12] Absorption of drugs from a tablet is determined by its release, pattern of dissolution and its permeability.[13] Hence, dissolution test of tablets in-vitro is very important to corelate with in-vivo effects prediction.[14]

Only the reliable quality of product can guaranty the efficacy and safety of medicine irrespective of dosage form.[15] The brand products of Aceclofenac SR available in the market are from both Nepalese companies and Indian companies. Products of different brand having the equal active pharmaceutical ingredients (API) may vary in their therapeutics effect due to differences in their bioequivalence.[16] Therefore, these brands might not be used interchangeable due to difference in biopharmaceutical equivalence. Availability of numerous brands may create selection dilemma in medical practitioners. Variation in clinical response to these brands have been reported due to availability of substandard fortified and counterfeit drugs also.[17] Thus, different brand products of same drugs require analysis for their biopharmaceutical equivalence to ensure their safety and efficacy. Quality assessment of locally available Aceclofenac SR tablet was not done by any researcher in Nepal. Therefore, this study conducted to analyze biopharmaceutical and physicochemical equivalence of Aceclofenac SR tablets manufactured by different manufacturer in Nepal.

Method

A cross-sectional study design was used.Study setting was Department of Pharmacy, Shree Medical and Technical College, Bharatpur, Chitwan, Nepal for three months (May-July 2020).

All reagents used were of analytical grade. Necessary chemicals and Aceclofenac SR tablets of various brands were purchased from the local market. Freshly prepared distilled water, analytical grade Potassium dihydrogen orthophosphate, Methanol and Sodium Hydroxide were used. Aceclofenac reference standard powder was obtained from Time Pharmaceutical Laboratory Pvt Ltd, Mukundapur, Nawalpur, Nepal. Eight different brands of Aceclofenac SR tablets, having label strength of 200mg were selected and purchased from registered retail pharmacies and these products were coded as A, B, C, D, E, F, G, and H. Manufacturing date, batch number and expiry date of tablets were checked before purchasing (**Table 1**).

Table 1: List of different brands of Aceclofenac SR tablets used in the study

Brand Code	Brand name	Mfg. date	Exp. date
A	Brand 1	Oct 2019	Sep 2021
B	Brand 2	Oct 2018	Sep 2020
C	Brand 3	Apr 2019	Mar 2021
D	Brand 4	Aug 2018	July 2020
E	Brand 5	Apr 2019	Mar 2021
F	Brand 6	Sep 2018	Aug 2020
G	Brand 7	Mar 2019	Feb 2021
H	Brand 8	Sep 2018	Aug 2020

The different brands of Aceclofenac SR tablets were subjected to the following assessments to assess their biopharmaceutical equivalence.[18-20]

(i) Physical Inspection: Purchased tablets were checked visually for their, brand name, color, size, shape. Whereas, the thickness and diameter were checked using digital vernier Caliper and later, the average and standard deviation was calculated.

(ii) Uniformity of weight: Using a digital analytical balance, the weight of 20 tablets of individual brand were taken individually. The average weight and % deviation of each tablet was determined:

$$\% \text{ deviation} = \frac{[\text{individual weight of a tablet} - \text{average weight of 20 tablets}]}{\text{average weight of 20 tablets}} \times 100$$

As per Indian Pharmacopoeia (IP), if average weight of tablets is more than 250mg, the maximum percentage deviation allowed should be ±5% for uniformity of weight test.

(iii) Hardness: The Monsanto hardness tester was used for Hardness test (the crushing strength of the tablets). Five tablets from individual brand were tested of the hardness and results were recorded. The average tablet hardness and standard deviation were calculated. Hardness of minimum 4 kg/cm^2 are required to withstand mechanical shocks for handling at any stage of manufacturing and transportation.[21]

(iv) Friability Test: This test is conducted to evaluate abrasion. The weighed 20 tablets of individual brand were subjected to a Roche friabilator test apparatus for abrasion testing using at 25 revolutions per minute. Later, dust was removed and tablets were re-weighed after 100 revolutions. The friability and % weight lost were calculated;

$$\% \text{ friability} = \frac{[\text{Initial weight} - \text{Final weight}]}{\text{Initial weight}} \times 100$$

(v) Assay (Drug Content): It is performed to check the content of active ingredient in each tablet**.** A fine powder was obtained by crushing of 20 weighed tablets of aceclofenac. About 100 mg of Acelclofenac from crushed powdered was dissolved in 50 ml of methanol in 100ml volumetric flask and volume were adjusted to the mark using methanol as solvent. Whatmann filter paper were used to filter the solution. Accurate 100 µg/ml concentration is obtained by diluting 10 ml of this filtrate and further diluted to 20 µg/ml. UV spectrophotometer was used to measure the absorbance of sample solution at 274nm. The standard graph obtained is used for calculation of % drug content. If the value obtained from assay are within the limits 85 to 115% of the average value, then the test tablets pass the assay.

(vi) In-vitro Dissolution Rate Determination: This is performed using USP type II apparatus in 900 ml phosphate buffer (pH 7.5) for 16thhrs. Water bath, maintained at 37±0.5°c was used for the dissolution medium and Paddle was adjusted to 50 rpm. About 5 ml samples were withdrawn at intervals of 1st, 4th 8th and 16th hours and released drugs were analyzed spectrophotometrically at 274nm. At each time of withdrawal, 5 ml of fresh dissolution medium were replaced into the dissolution flask.

(vii) Preparation of Calibration Curve: UV-visible Spectrophotometric method of analysis at λ_{max} 273nm was developed with the help of calibration curve. A stock solution of concentration 20µg/ml Aceclofenac was prepared in a phosphate buffer of pH 7.5. Solutions of concentration (4, 8, 12, 16 and 10 µg/ml) were made from stock solution with appropriate dilutions. Using UV spectrophotometry absorbance was taken at the λ_{max} 273nm. A plot was drawn with given value of absorbance that shows correlation between concentration and absorbance.[22]

The data's obtained were entered into Microsoft Excel 2016 and checked for its correctness and completeness. Descriptive statistics mean, standard deviation, frequency and percentage were calculated using Microsoft Excel 2016. The data were presented as tables and graphs.

Result

Pharmaceutical product related information was recorded. The calibration curve was plotted from the obtained the values of concentration verses respective absorbance for each of the concentration of 4, 8, 12, 16 and 20µg/ml of standard Aceclofenac. This analysis for linearity showed that the solvent used for testing Aceclofenac SR tablet and in-vitro drug release were suitable and had no interference while obtaining absorbance in UV visible spectrophotometer. From the curve, the value for correlation coefficient (R^2) was found to be 0.998 in phosphate buffer pH 7.5 which shows linearity as the value is near to 1. The plotted calibration curve for Aceclofenac in phosphate buffer as solvent is given in Figure 1.

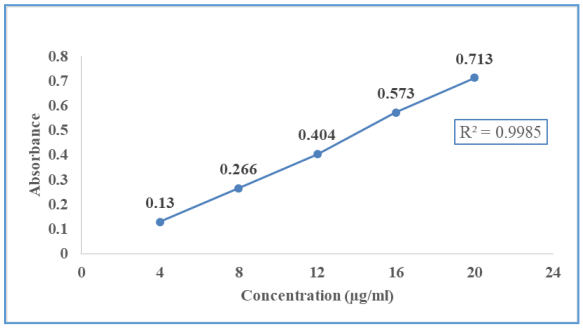

Figure 1: Standard calibration curve of absorbance of Aceclofenac SR tablet in 7.5 pH phosphate buffer

On physical inspection, all tablets were white in color and oval in shape and three brands (code A, C and H) were uncoated (**Table 2**).

Table 2: Physical aspects examination of the different brands of Aceclofenac SR tablets

Brand code	Colour	Shape	Coating
A	White	Round	Uncoated
B	White	Round	Film coated
C	White	Round	Uncoated
D	White	Round	Film coated
E	White	Round	Film coated
F	White	Round	Film coated
G	White	Round	Film coated
H	White	Round	Uncoated

The mean weight of tablets Aceclofenac SR from different manufacturer is given in **Table 3**. Brand F had minimum average weight (301±1.70mg) whereas brand H had maximum average weight (428±12.91mg). The maximum standard deviation was seen in brand H and minimum in brand E. The variation in weight of tablets of different manufacturer ranged within the maximum limit of ±5% except brand H.

Table 3: Weight variation of different brands of Aceclofenac SR tablets

Parameters	Weight of different brand of Aceclofenac SR tablets (mg)							
	A	B	C	D	E	F	G	H
Mean	422	426	333	319	405	301	395	428
SD	3.57	4.4	3.38	6.16	1.34	1.700	4.73	12.91
Minimum	417	417	331	310	402	297	384	407
Maximum	429	413	340	332	407	303	400	466

Physiochemical Parameters tablets Aceclofenac SR from different manufacturer is given in **Table 4**. The thickness of different Aceclofenac SR tablets varied with brands ranging from 4.002±0.0044 mm to 5.42±0.016 mm. All of the brand tablets had the recommended hardness (≥4Kg/cm^2). The Brand B had a maximum hardness (17.7±0.44 kg/cm^2) while brand A had minimum hardness (9.6±0.82 kg/cm^2). Brand D had higher deviation of 3.00 and brand E had a smaller deviation of 0.22. Brand C had maximum friability (0.10%) and brand A had a minimum friability (0.01%). The friability values of all products were within the recommended specification (≤1%). All tablets passed the test for assay as the amount of drug in each tablet was in the range of 85% - 115%. Brand A had maximum assay value (105.51±6.93) and brand F had a minimum value (90.10±1.46) (**Table 4**).

Table 4: Physiochemical Parameters of different brands of Aceclofenac SR tablets

Brand Code	Thickness (mm) (n=5)	Diameter (mm) (n=5)	Hardness (Kg/cm^2) (n=5)	Friability (%)	Content of active ingredient (%) (n=3)
A	4.34±0.012	11.074±0.008	9.6±0.82	0.011	105.51±6.93
B	4.27±0.018	11.27±0.0083	17.7±0.44	0.000	93.22±1.89
C	4.002±0.004	11.128±0.008	15.6±0.96	0.105	96.06±3.72
D	4.04±0.039	11.9±3.008	11.9±3.01	0.000	99.31±2.17
E	4.52±0.037	11.30±0.046	16.4±0.22	0.000	94.75±13.50
F	4.52±0.016	10.9±1.410	10.9±1.41	0.000	90.10±1.46
G	5.42±0.016	12.7±0.410	12.7±0.44	0.000	92.73±0.42
H	4.87±0.111	9.76±2.220	9.76±2.22	0.030	92.23±1.09

The cumulative amount of Aceclofenac released at different time intervals (1st, 4th, 8th and 16th hrs) is shown in **Figure 2**. Brand C has highest released drug of 109.55±3.09 % and brand H had lowest drug released of 63.88±3.71% at 16 hrs. The % drug release of all brands was in the range of 50 – 80% except brand E & H showed 63.88% drug release at 8thhour.

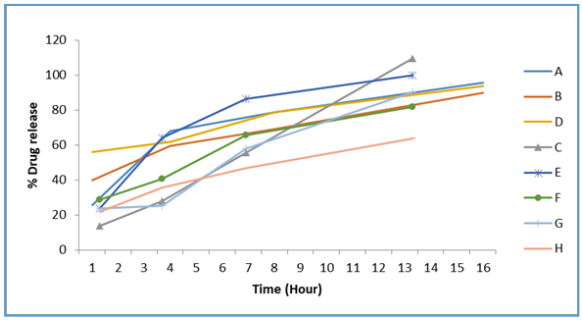

Figure 2: Dissolution Profile of the eight tested different brands of Aceclofenac SR Tablets

Release kinetics of Aceclofenac SR tablets is shown in **Table 6**. The brand A, B and H followed Pappes release kinetic model whereas brand C followed zero order kinetic model, brand D and G followed first order kinetic model and brand E & F followed Higuchi model.

Table 6: Release kinetics of Aceclofenac SR tablets

Brand code	R^2 value			
	Zero order	First order	Higuchi	Pappas
A	0.00	0.648	0.871	0.934
B	0.862	0.887	0.684	0.993
C	0.990	0.943	0.849	0.968
D	0.574	0.950	0.270	0.901
E	0.247	0.666	0.918	0.915
F	0.227	0.883	0.939	0.457
G	0.850	0.916	0.890	0.803
H	0.158	0.890	0.956	0.996

The price of different brand of Aceclofneac SR tablets per strip (one strip=10 tablets) is shown in **Figure 3**. Brand E had maximum retail price whereas brand D and E had lowest retail price.

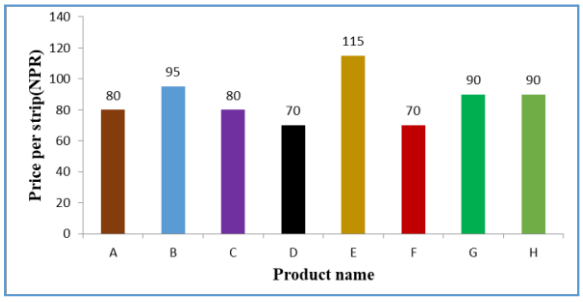

Figure 3: Price variation among different brand of Aceclofenac SR tablets in Nrs

Discussion

All the tablets from different manufacturer passed the uniformity of weight and all complied with the international standard as the weight variation of all brands ranged within the maximum limit of ±5% except brand H. Hence, only seven brands of Aceclofenac tablets conformed to the specifications. All of the brand tablets had the recommended hardness (≥4Kg/cm^2). A friability value of less than 1% is desirable for the tablets of good quality.[23] The results friability test of Aceclofenac tablets showed the friability values within the recommended specification (≤1%). Therefore, all brands of Aceclofenac tablets were mechanically stable as all met the recommended standard.[23]It was interesting to find out that all eight brand of Aceclofenac SR tablet had the values of drug content within the standard specification limit of 90-110%.[24]Most of the brands showed drug release more than 80% at 16th hrs showing sustained release except brands H that showed only 63.88% drug release. According to the data it has been found that price does not causes to make the product better. Drug release kinetics showed more or less same release kinetics of expensive and cheap products of Aceclofenac. Hence low priced drugs can be used interchangeable with the expensive drugs. The study has some limitations. The sample size was small. The drug release in-vitro is a likely prediction but not necessarily that formulations will perform similarly in-vivo.

Conclusion

All of the brands of Aceclofenac SR tablets passed the physical inspection test, uniformity of weight test, hardness test, friability test, content uniformity assay. Only seven brands of Aceclofenac passed dissolution test and hence they can be substituted with one another. The study findings highlight that one brand products of Aceclofenac available in the market did not meet up to the required biopharmaceutical specifications

Recommendation

Post marketing product assessment should be carried out regularly in order to ascertain the quality of drug products being sold in the market. In-vivo bioequivalent studies can be conducted to confirm the quality of the brands of Aceclofenac SR tablets.

Conflict of interest

The author declares no conflict of interest.

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